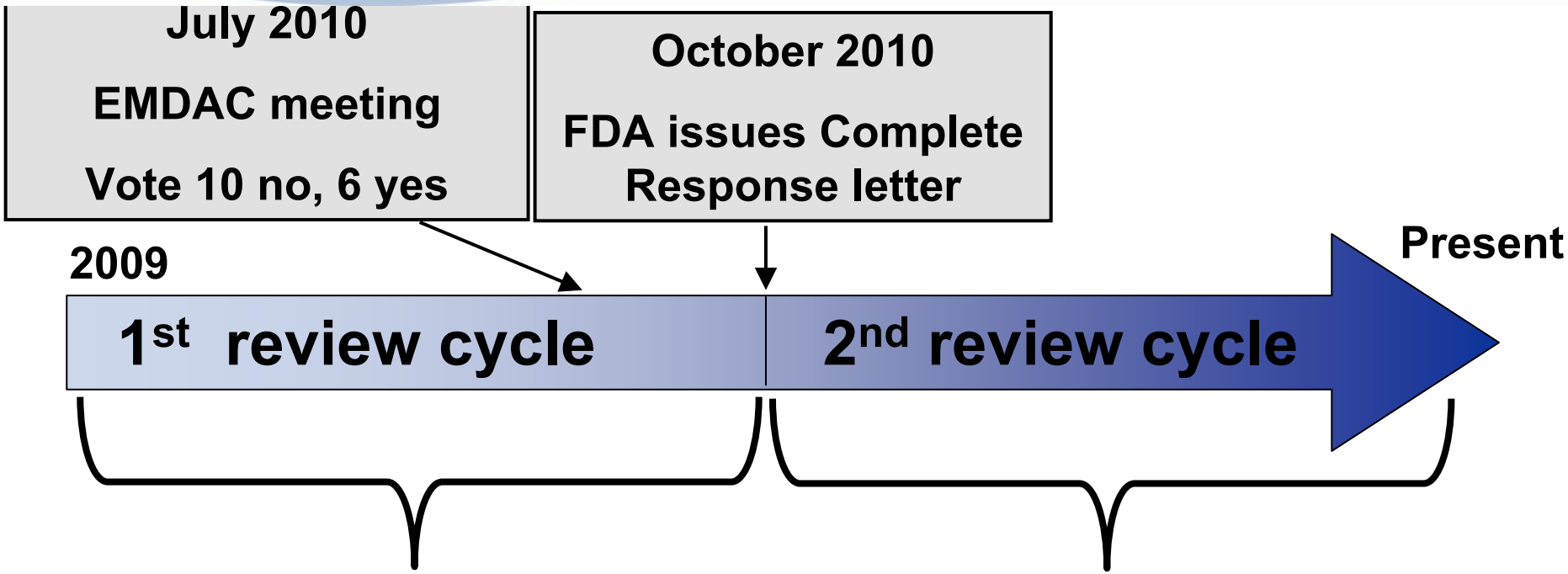
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Silver Spring, Maryland
February 22, 2012

QNEXA (Phentermine/Topiramate) NDA 22580

Mary Dunne Roberts, MD
Division of Metabolism and Endocrinology Products



- Pivotal Phase 3 trials
  - Study OB-301
    - 28 weeks, factorial design
  - Study OB-302
    - 56 weeks, BMI ≥35 kg/m^2
  - Study OB-303
    - 56 weeks, 2+comorbidities

- Complete response
  - Study OB-305
  - Cardiovascular risk
  - Teratogenicity risk

Efficacy Conclusions

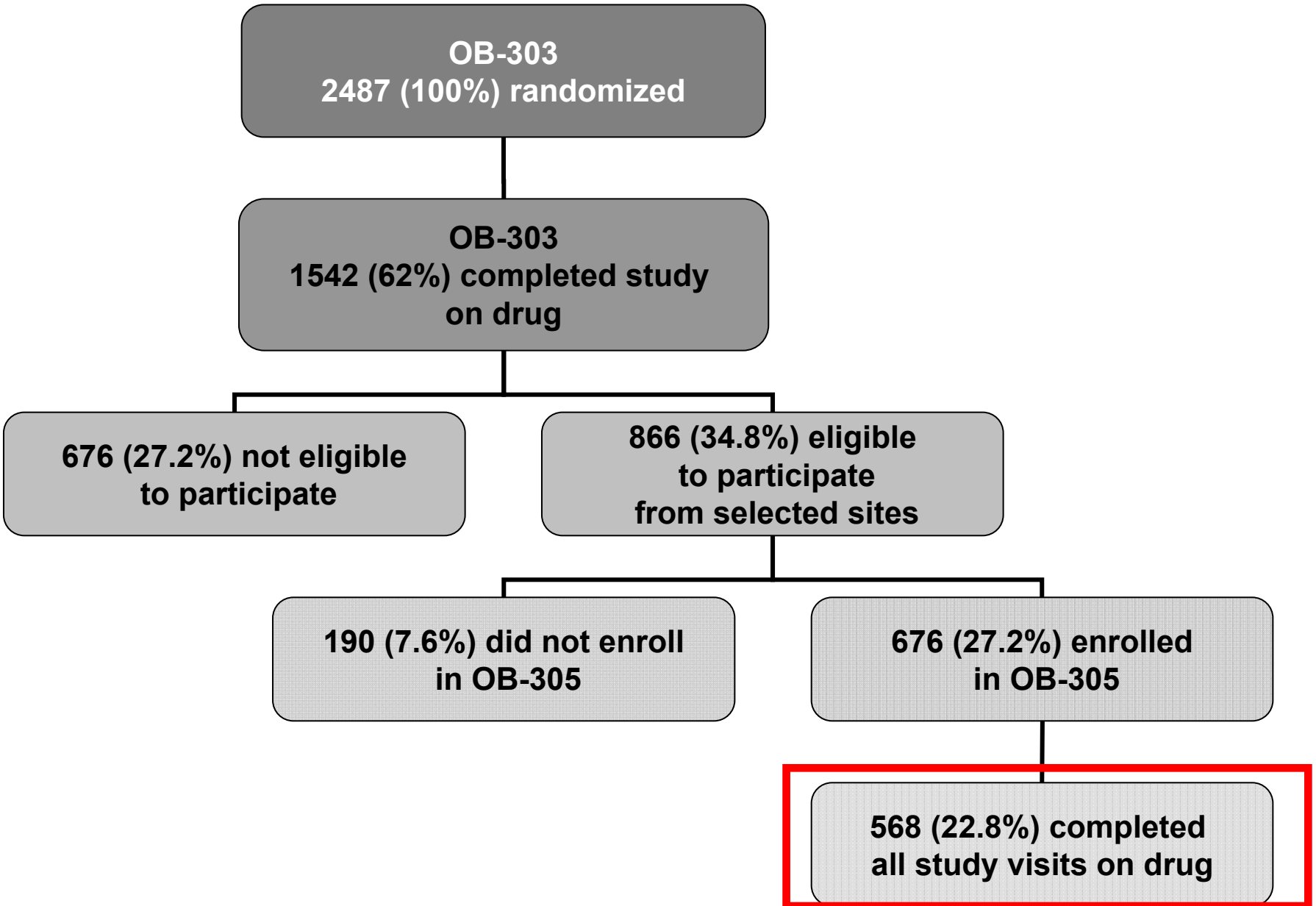
- Study OB-301 satisfied fixed-dose combination guidance
- Study OB-302 and OB-303 met FDA 1-year efficacy benchmarks
- PHEN/TPM associated weight loss was accompanied by improvements in waist circumference, blood pressure, lipids, and HbA1c

Submitted to PHEN/TPM Application

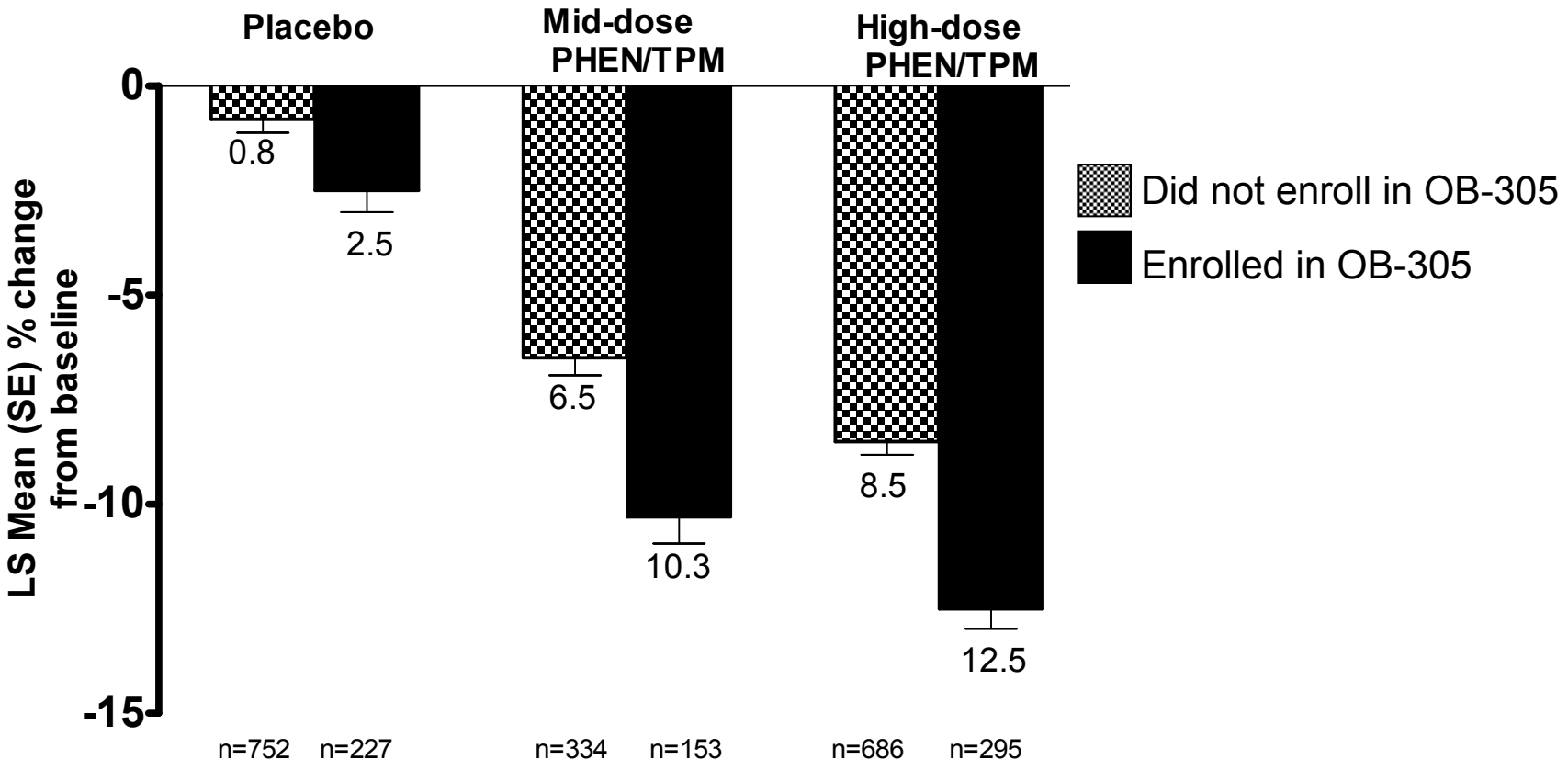
- Study OB-305
  - 52-week extension study of eligible subjects from selected sites in OB-303
- CV risk analysis
  - Analysis of 1-year safety cohort
  - Overnight heart rate monitoring: OB-204
  - Post-hoc major adverse cardiovascular event (MACE) analysis
- Teratogenicity
  - Pregnancy registries
  - Applicant funded retrospective cohort studies
    - Wolters Kluwer
    - FORTRESS
  - Two case-control studies from surveillance programs
    - Slone Epidemiology Center
    - CDC

Study OB-305

Disposition of Subjects from OB-303 into OB-305



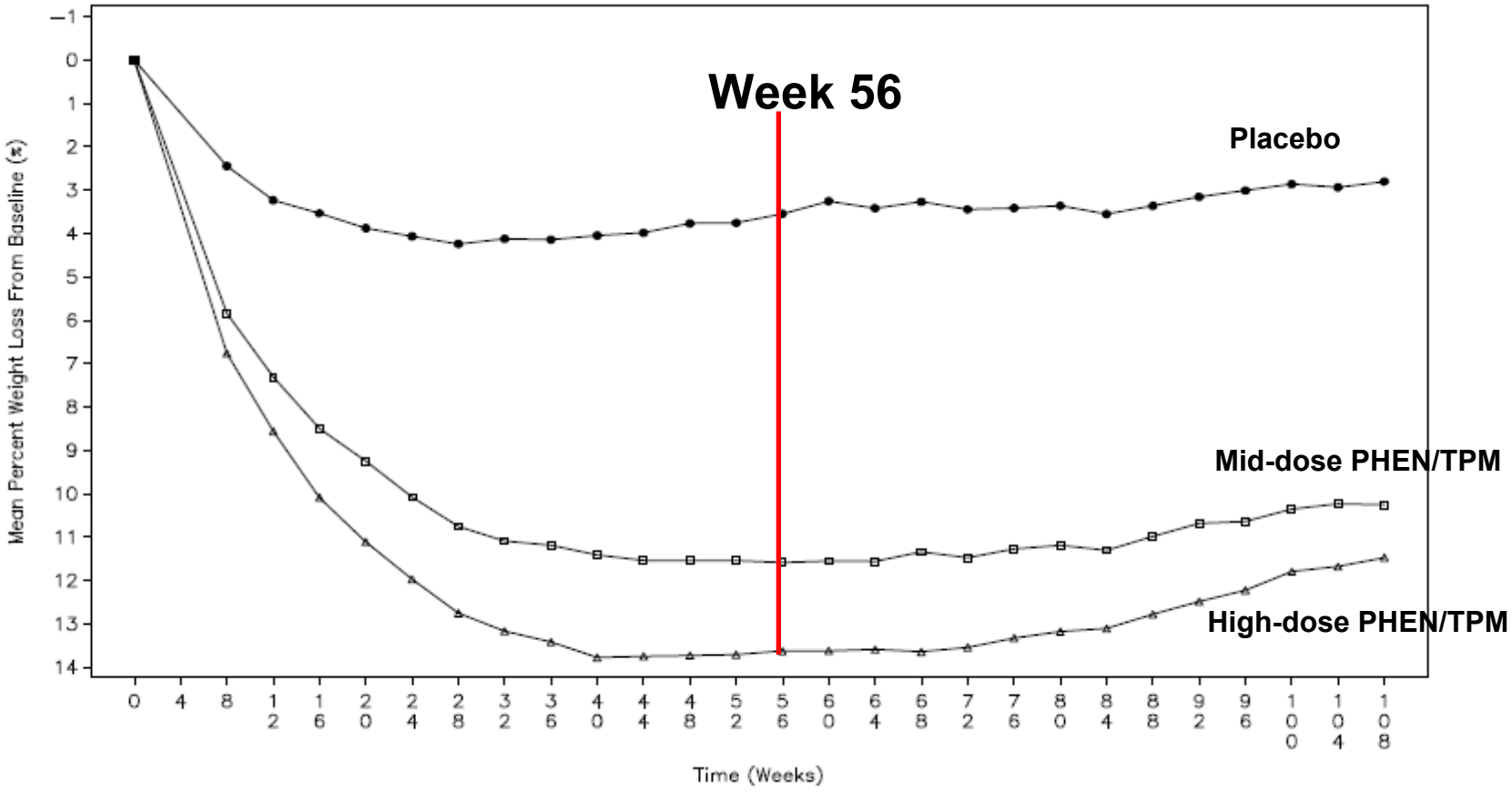
Percent Change in Body Weight (Week 56)



Primary Weight Loss Endpoints Week 108 (LOCF)

	Treatment group	LS Mean % wt loss from baseline	LS Mean diff (95% CI)	% achieving ≥5% wt loss
OB-305	Placebo	1.8	--	30.0%
	Mid-dose PHEN/TPM	9.3	7.5	75.2%
	High-dose PHEN/TPM	10.5	8.7	79.3%

Weight Loss Over Time: OB-305 (on drug at time of measurement)



Weight-related Comorbidities: OB-305

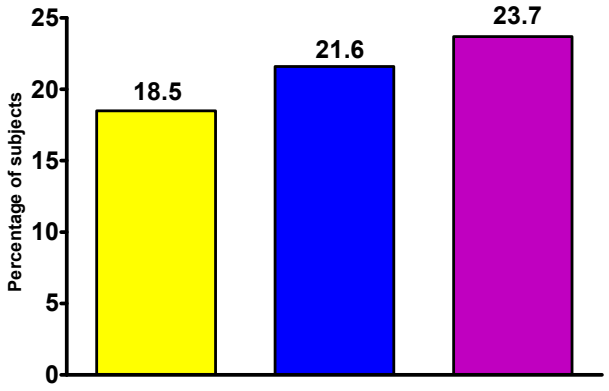
Baseline to Week 108 – ITT LOCF	LS mean Mid-dose treatment difference from placebo	LS mean High-dose treatment difference from placebo
Waist circumference (cm)	-6.2	-7.0
Systolic blood pressure (mmHg)	-1.5	-1.1
Diastolic blood pressure (mmHg)	+0.1	+0.4
LDL-C (%)	+6.1	+5.1
Triglycerides (%)	-12.9	-14.1
HDL-C (%)	+2.5	+7.1
HbA1c (%)	-0.2	-0.2

	Placebo	Mid-dose	High-dose
Incidence of new T2DM	7.0%	3.2%	1.7%
Decrease in HTN meds	7.5%	13.1%	15.6%

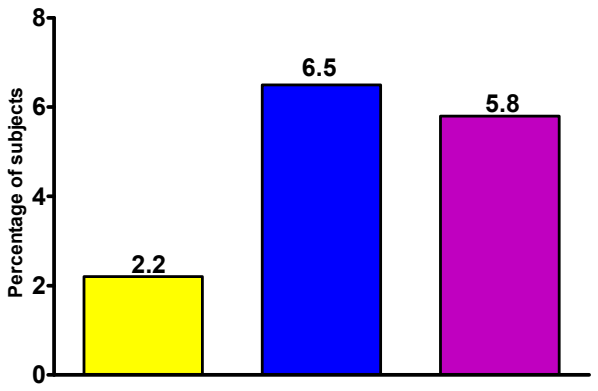
OB-305 Efficacy Conclusions

- **In a small non-randomized cohort of eligible patients based on compliance**
  - Treatment with PHEN/TPM resulted in greater weight loss at two years compared to placebo
  - All treatment groups experienced weight regain in the second year
  - Relative to placebo
    - Blood pressure treatment differences were similar
    - Favorable changes in anti-hypertensive medications
    - Favorable changes in HDL-C and triglycerides (but not LDL-C)
    - Favorable changes in HbA1c and progression of new-onset of type 2 diabetes
- **Important to consider the study design limitations when interpreting results**

Safety Events of Interest: Two-year Cohort



Psychiatric disorders

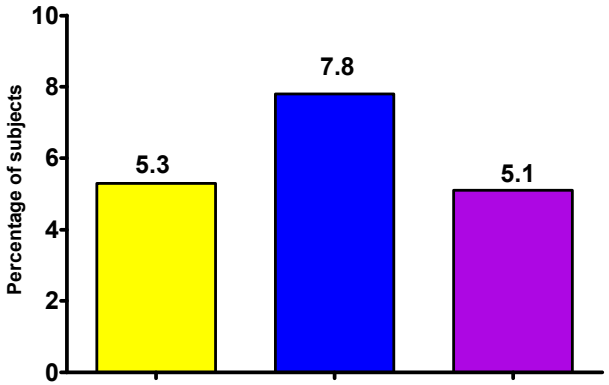


Cognitive disorders

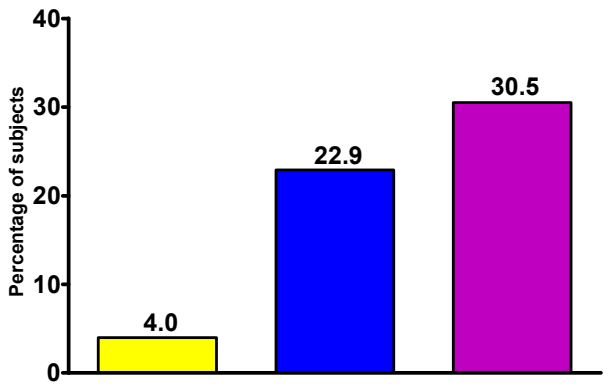
Placebo

Mid-dose PHEN/TPM

High-dose PHEN/TPM



Cardiovascular disorders



Bicarb <21 mEq/L

General Safety: OB-305

- Safety data from 52-week extension study, OB-305, consistent with safety profile observed in 1-year safety cohort

- PHEN/TPM-treated subjects experienced higher incidence of the targeted medical events related to psychiatric, cognitive, cardiac disorders, and reductions in serum bicarbonate

Cardiovascular Risk

Baseline Cardiovascular-related Medical Conditions 1-year cohort

	Placebo N=1561	Mid-dose PHEN/TPM N=498	High-dose PHEN/TPM N=1580
CV disease	14.6%	14.9%	16.1%
Dyslipidemia	25.6%	36.1%	26.3%
Hypertension	40.2%	52.4%	40.6%

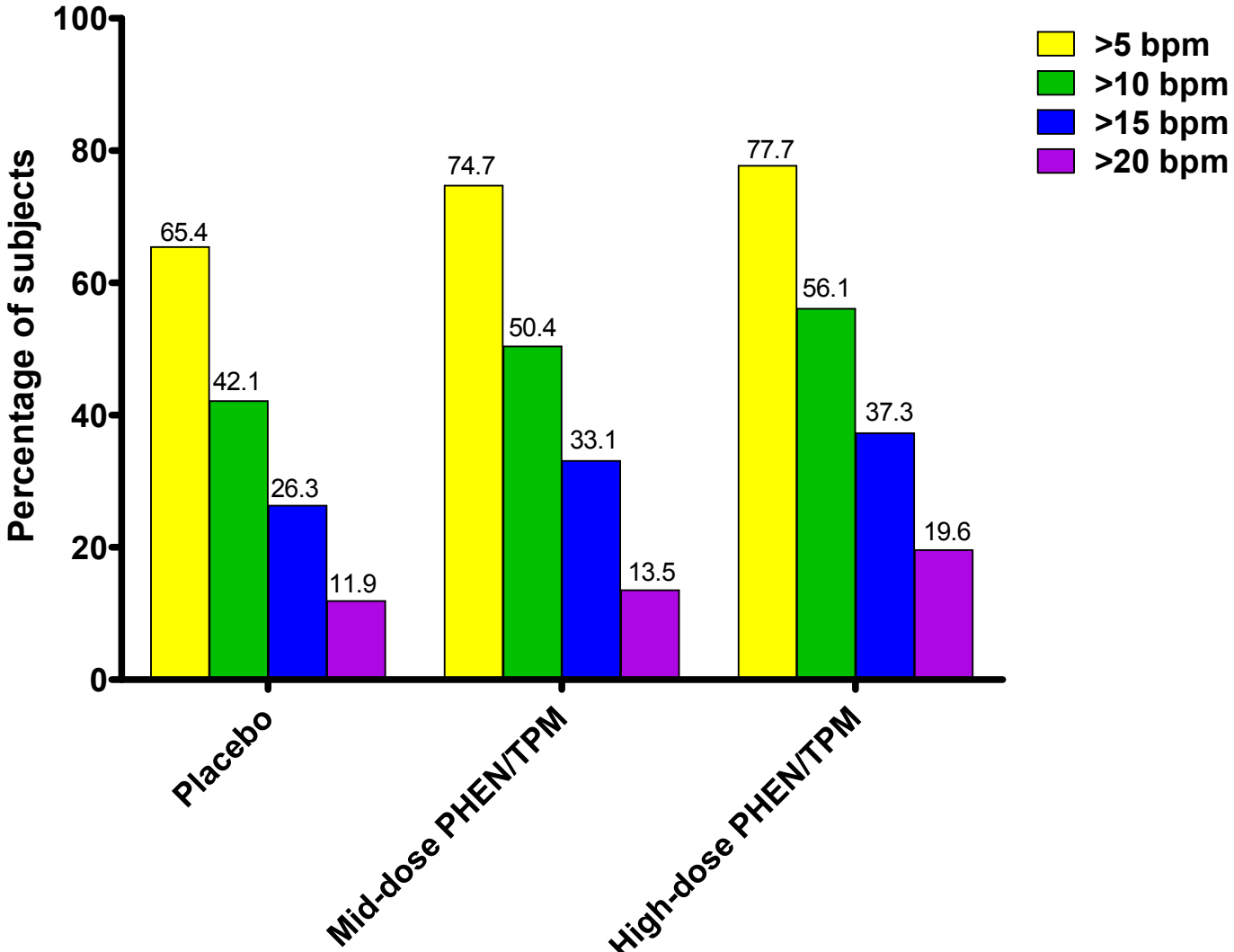
- Includes subjects from OB-302, OB-303, OB-202/DM-230 (n=3879)

- **CV disease:** having either (1) a history of CAD, peripheral arterial occlusive disease, or stroke; or (2) diabetes plus ≥1 of the following: current smoker, hypertension, or dyslipidemia

Mean (SD) Change in BP and HR
1-year Cohort from Baseline to Study Exit

	Placebo N=1561	Mid-dose PHEN/TPM N=498	High-dose PHEN/TPM N=1580
n (subjects with baseline and endpoint measurement)	1532	488	1553
SBP	-2.1 (14.0)	-5.2 (14.8)	-5.2 (14.5)
p-value compared to placebo	----	<0.0001	<0.0001
DBP	-1.9 (9.6)	-3.3 (9.9)	-2.9 (9.4)
p-value compared to placebo	----	0.0044	0.0023
Heart rate	0.0 (10.2)	+0.6 (10.2)	+1.6 (10.3)
p-value compared to placebo	----	NS	<0.0001

Categorical Change in HR 1-year Cohort



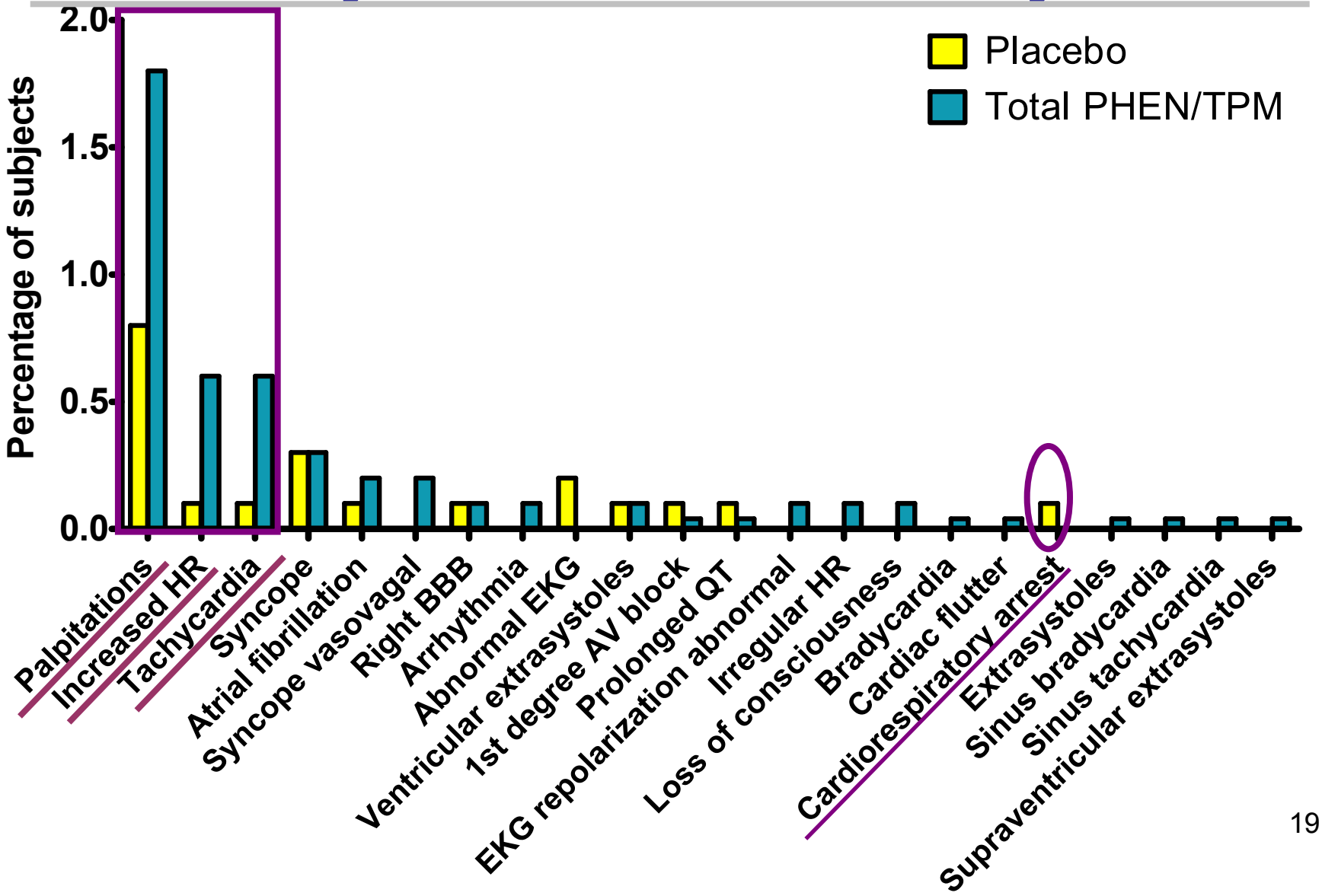
Change in Rate-Pressure Product* at Week 56 (LOCF) from Baseline 1-year Cohort

	Placebo N=1561	Mid-dose PHEN/TPM N=498	High-dose PHEN/TPM N=1580
n	1531	488	1551
Baseline (Mean)	9.16	9.27	9.14
LS mean change at Week 56	-0.13	-0.23	-0.18
p-value compared to placebo	----	NS	NS

***RPP=SBP x HR / 1000**

n is the number of subjects with values at both time points

Cardiac Arrhythmia Subclass Terms1-year Cohort



CV Safety: Heart Rate Outliers

Mean (SD) Change in BP and HR 1-year Cohort at Week 56/ET from Baseline Heart Rate Outliers*

	Placebo	Mid-dose PHEN/TPM	High-dose PHEN/TPM
n	284	132	488
SBP	-2.5 (14.9)	-4.3 (16.3)	-6.6 (14.4)
DBP	-2.0 (10.0)	-3.2 (11.1)	-3.3 (9.6)
Heart rate	+7.9 (9.9)	+6.1 (11.7)	+8.3 (9.5)
RPP	+0.80 (1.7)	+0.44 (1.9)	+0.52 (1.7)

***Subjects with increase in HR >10 bpm over baseline at 2 or more consecutive visits or having a HR >90 bpm at 2 or more consecutive visits**

n is the number of subjects with baseline and endpoint measurements ET=early termination

CV Safety: 2-year Cohort

Baseline Cardiovascular-related Medical Conditions 2-year Cohort

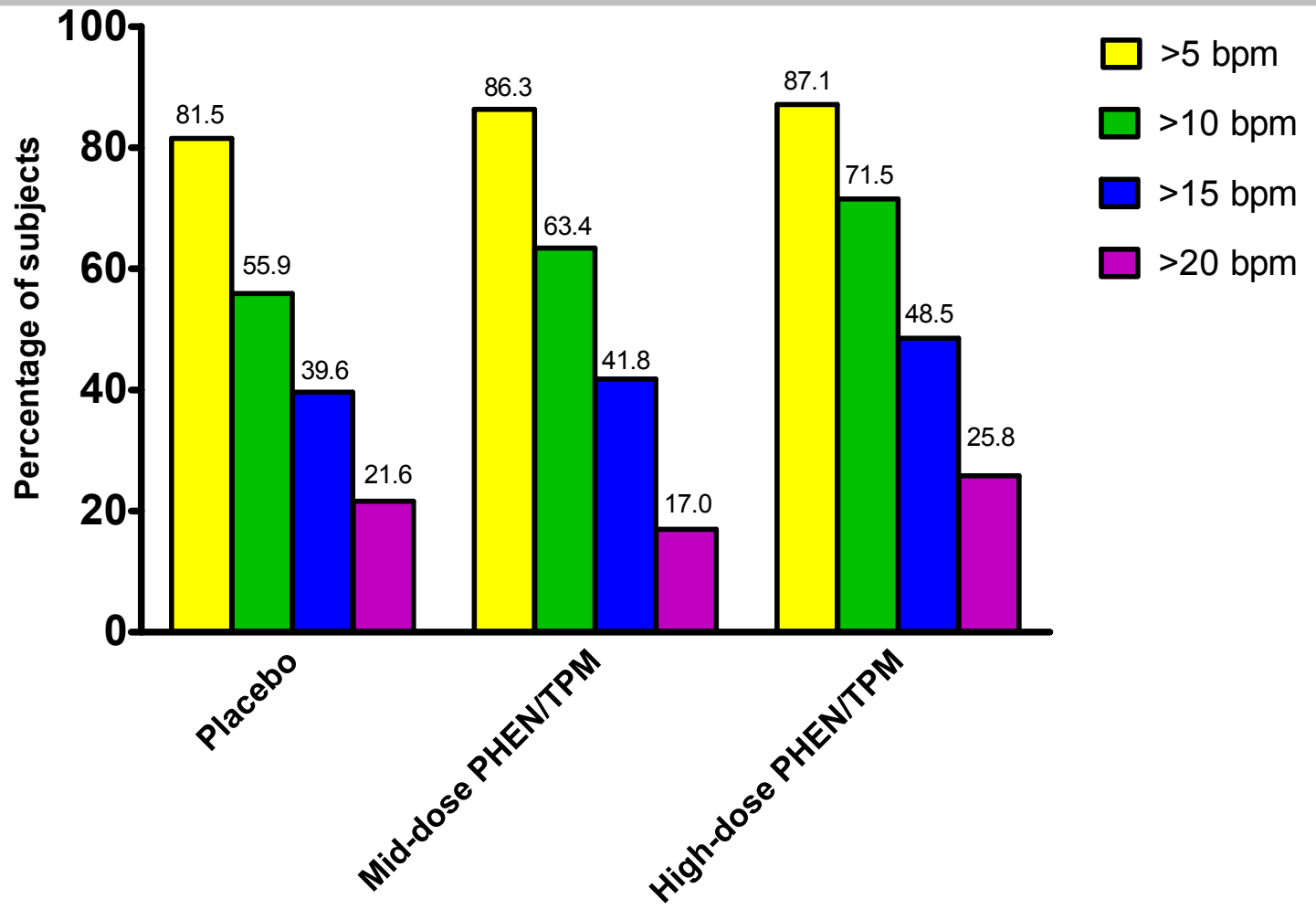
	Placebo N=227	Mid-dose PHEN/TPM N=153	High-dose PHEN/TPM N=295
CV disease	24.2%	17.0%	23.4%
Dyslipidemia	35.2%	31.4%	35.6%
Hypertension	52.9%	46.4%	52.2%

Mean (SD) Change in BP and HR 2-year Cohort at Week 108 from Baseline

	Placebo N=227	Mid-dose PHEN/TPM N=153	High-dose PHEN/TPM N=295
n	197	129	248
SBP	-4.2 (15.1)	-5.0 (14.3)	-3.9 (14.0)
DBP	-3.6 (10.3)	-3.5 (9.6)	-2.9 (9.4)
Heart rate	+0.4 (9.9)	+1.3 (10.2)	+1.7 (10.6)
RPP	-0.22	-0.20	-0.06

n is the number of subjects with measurements at both Baseline and Week 108

Categorical Change in HR
2-year Cohort



Study OB-204

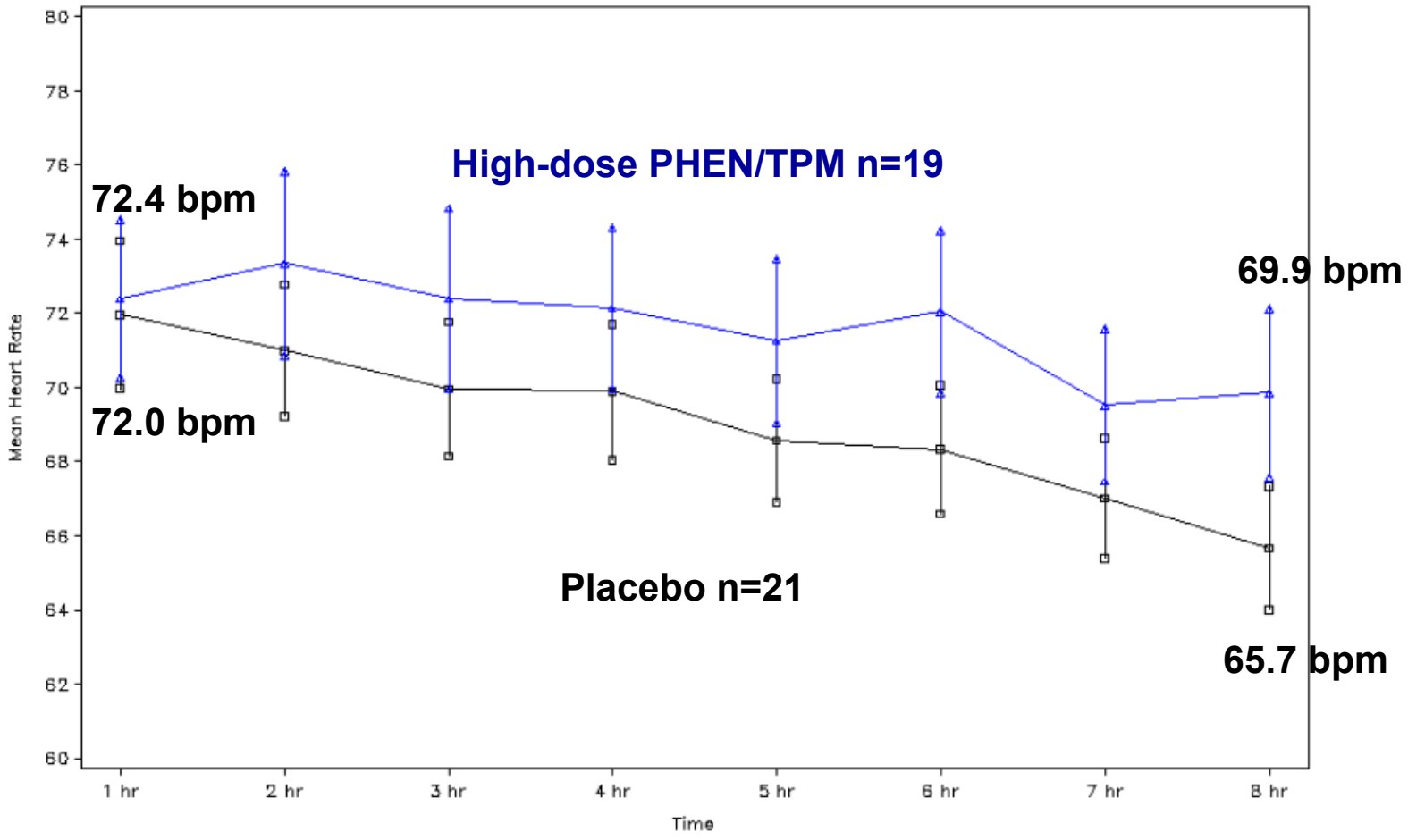
Study OB-204

- 28 week study of 45 subjects with moderate to severe obstructive sleep apnea
  - Mean age 52.4 years, 53.3% Male, 91% Caucasian
  - Mean BMI 35.6 kg/m^2
  - Mean apnea/hypopnea index 44 to 45
  - Randomized to placebo or high-dose PHEN/TPM
  - Overnight polysomnogram (PSG) Baseline/Week 28

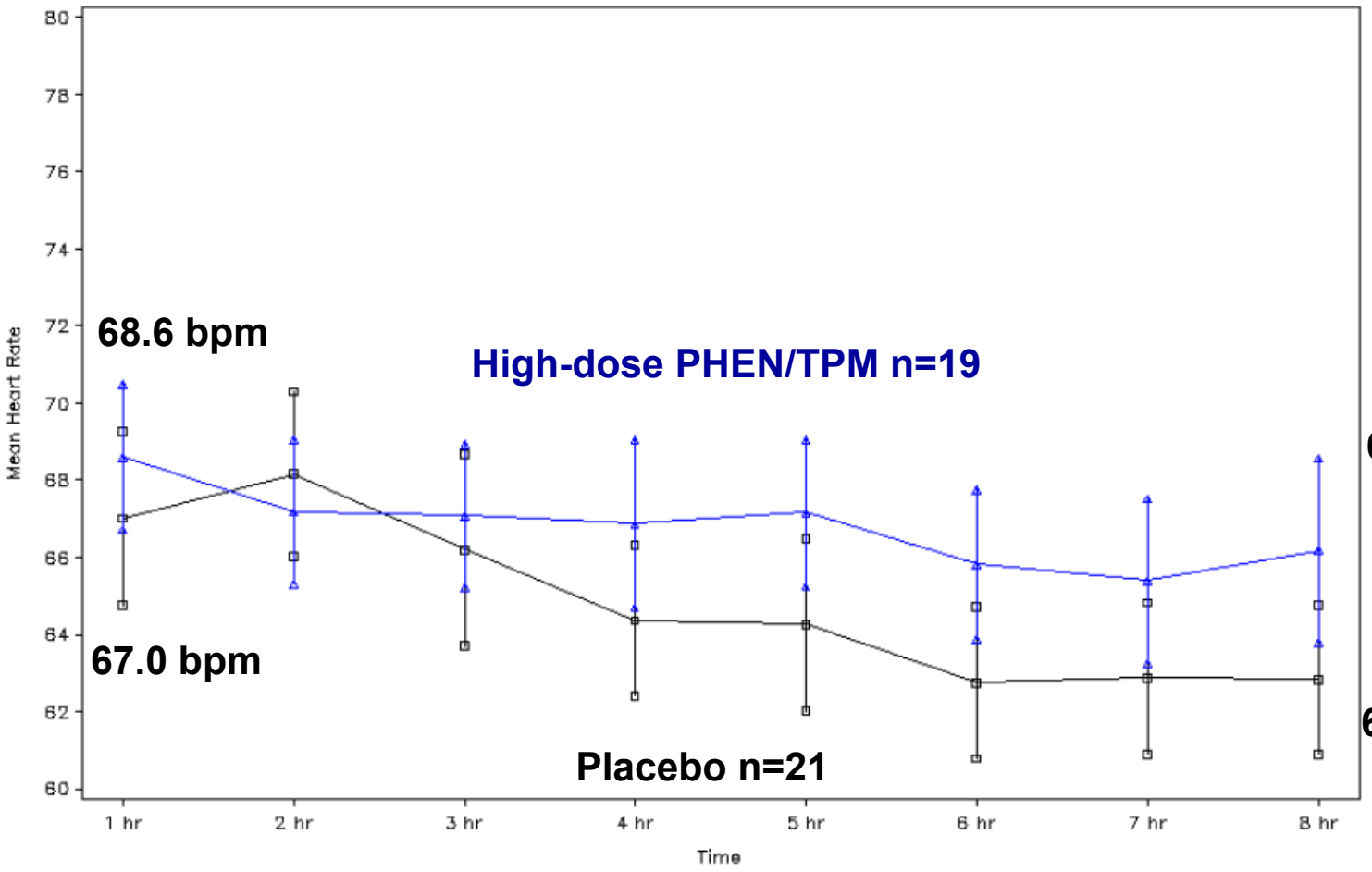
Heart Rate Measurements: OB-204

	Placebo		High-dose PHEN/TPM	
	Baseline n=21	**Week 28 n=21**	**Baseline n=19**	**Week 28 n=19**
Mean overnight (8 hours) heart rate (bpm) by PSG	68.1	64.8	71.6	66.9
	Baseline n=23	**Week 28 n=23**	**Baseline n=22**	**Week 28 n=22**
Heart rate (bpm) Week 28 with LOCF	72.1	73.7	71.8	79.7

Baseline PSG Mean Heart Rate



Week 28 PSG Mean Heart Rate



Major Cardiovascular Event (MACE) Analysis

MACE Analysis

- Clinical development program not designed to seek a cardiovascular prevention indication
- Study trials not powered to evaluate the effect of PHEN/TPM on CV outcomes
- Recruitment of an appropriate at-risk population, prespecification of MACE, and *a priori* adjudication of MACE was not done

MACE

- MACE: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke
- HR 0.84 (95% 0.26, 2.64)

Preferred term	Sponsor adjudication	Placebo N=1742	PHEN/TPM N=2581
Cardio-respiratory arrest	CV death	1	0
Myocardial infarction/Acute MI	Myocardial infarction/coronary revascularization	0	6
Cerebrovascular accident Intracranial hemorrhage Brain stem infarction Cerebral infarction	Stroke	4	1
Total subjects		**5 (0.29%)**	**7 (0.27%)**

Cardiovascular Safety

- Palpitations and tachycardia were the most common terms reported in cardiac arrhythmia subclass
- Ischemic events were too few in number to draw definitive conclusions regarding PHEN/TPM and its effect on major cardiovascular events
- Long term effects of decrease blood pressure and increase heart rate change in an at-risk obese population uncertain
- PHEN/TPM cardiovascular outcomes trial proposed

Teratogenicity

Label Changes

- March 2011: Drug safety communication for TOPAMAX (topiramate)
  - Epilepsy
  - Migraine prophylaxis
- North American AED Pregnancy Registry
  - Oral clefts prevalence 1.2%
  - Relative risk of 9.6 (95% CI 3.6-25.7) compared to population of untreated women
- Topiramate label changed pregnancy category from C to D
  - C: animal studies adverse effect on fetus, no human data, benefits may outweigh risks
  - D: human studies adverse effect on fetus, benefits may outweigh risk
- Phentermine label changed to pregnancy category X
  - X: animal or human studies adverse effects on fetus, risks outweigh benefit

PHEN/TPM and Pregnancy

- Participation required:
  - Agreement to use double-barrier or OCP + single barrier
  - Monthly negative urine pregnancy test
- 34 pregnancies during PHEN/TPM clinical development program
  - 19 pregnancies delivered
  - 6 elective terminations
  - 6 spontaneous terminations
  - 1 ectopic
  - 1 unknown
  - 1 lost to follow-up

PHEN/TPM and Pregnancy

- Majority occurred in high-dose group
- 13 pregnancies with OCP as the reported method of contraception
- All discontinued drug
- Average gestational age 5.4 weeks at diagnosis
- No anomalies noted

Acknowledgments

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Review of Studies on Topiramate (TPM) Use in Pregnancy and Risk of Oral Clefts (OCs) and Major Congenital Malformations (MCMs)

Endocrinologic and Metabolic Drugs Advisory Committee Meeting on Qnexa
February 22, 2012

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Outline

- Background
- Study summaries
- Study limitations
- Conclusions

Risk Factors of Oral Clefts

- Smoking
- Alcohol
- Family history of clefts
- Infant born with other malformations
- Asian > Caucasians > African
- Folic acid deficiency
- Maternal illness
  - Diabetes
  - Infectious disease
- Maternal age
  - Teenager
  - Over 35 years old
- Teratogens
  - Medications
  - Radiation
  - Chemicals

Studies of Topiramate Use and Risk of OCs and MCMs

- Slone/CDC study (abstract)
  - Use of topiramate in pregnancy and the risk of oral clefts
  - by Margulis, et al.
- Denmark study (publication)
  - Newer-generation antiepileptic drugs (AEDs) and the risk of major birth defects
  - by Molgaard-Nielsen, et al.
- Wolters Kluwer study (2 abstracts & sponsor's report)
  - Retrospective analysis of major congenital malformations (MCMs) and oral clefts (OCs) associated with in utero topiramate exposure,
  - funded by Vivus
- Fetal outcomes retrospective topiramate exposure study (FORTRESS) (interim report & response to FDA's information request)
  - funded by Vivus

Slone/CDC Study

- Study design
  - Pooled case-control study
- Data sources
  - Slone Epidemiology Center Birth Defects Study (BDS, 1997-2009)
  - CDC's National Birth Defects Prevention Study (NBDPS, 1996-2007)
- Study groups
  - Cases
    - Oral clefts (n=3,034)
    - Major congenital malformations (n=33,605)
  - Controls
    - Non-malformed (n=15,367)

Slone/CDC Study Results

- Pooled odds ratios
  - Oral clefts
    - Cleft lip with or without cleft palate
      - **5.36 (95% CI, 1.49-20.07)**
    - Isolated cleft palate
      - No cases in topiramate-exposed pregnancies
  - Major congenital malformations
    - **1.01 (95% CI, 0.37-3.22)**

Denmark Study

- Study design
  - Retrospective cohort study
- Data sources (1996 – 2008)
  - Danish Medical Birth Registry
  - Registry of Medicinal Product Statistics
  - National Patient Registry
- Study cohorts
  - **Newer-generation AEDs** -exposed cohort (n=1,532)
    - **TPM-exposed cohort (n=108)**
      - Monotherapy
      - Polytherapy with other AEDs
  - Unexposed to any newer-generation AEDs (n=836,263)

Denmark Study Results

- Prevalence odds ratio
  - Major congenital malformations
    - **5 cases** of MCMs
    - **1.44 (95% CI, 0.58-3.58)**
      - Adjusted for exposure to older-generation AEDs & diagnosis of epilepsy
  - Oral clefts
    - **1 case** of oral cleft
    - **5.45 (95% CI, 0.77-38.36)**
      - Crude estimate by FDA based on data reported in publication

Wolters Kluwer Study (sponsored by Vivus)

- Study design
  - Retrospective cohort study
- Data source
  - Wolters Kluwer Source Lx Patient data (2003-2010)
- Study cohorts
  - TPM-exposed cohort (n=870)
  - Unexposed cohorts:
    - Other anti-epileptic drug-exposed cohort (n=3,615)
    - Epilepsy cohort (n=2,607)
    - Migraine (no epilepsy) cohort (n=26,865)
      - Treated migraine (no epilepsy) cohort (n=2,526)
    - Diabetes cohort (n=13,063)

Wolters Kluwer Study Results

Topiramate vs.	OCs RR (95% CI)	MCMs RR (95% CI)
Other AEDs	1.39 (0.28-6.85)	1.33 (0.92-1.90)
Epilepsy	0.75 (0.16-3.52)	0.98 (0.68-1.41)
Migraine	1.47 (0.36-6.06)	1.12 (0.81-1.55)
Treated Migraine	0.95 (0.19-4.68)	0.99 (0.68-1.42)
Diabetes	0.88 (0.21-3.67)	0.65 (0.47-0.89)

- Unadjusted relative risks
- No statistically significant higher risks of OCs or MCMs

FORTRESS Study (sponsored by Vivus)

- Required by FDA
- Study design
  - Retrospective cohort study
- Data sources (1997-2010/2011)
  - OptumInsight Normative Health Information Database (n=748)
  - Thomson Reuters MarketScan Multi-State Medicaid Research Database (n=583)
  - HealthCore Integrated Research Database (n=495)
  - Kaiser Northern California Research Database (n=119)

FORTRESS Study Cohorts

- TPM-exposed cohort (n=1,945)
  - TPM monotherapy subgroup (n=1,740)
- Unexposed cohorts
  - **Formerly Exposed (FE)** cohort (n=13,512)
    - Exposed to TPM or other AEDs up to 120 days before pregnancy
    - No TPM or other AEDs exposure within 120 days before or during pregnancy
  - **Similar Medical Profile (SMP)** cohort (n=252,597)
    - TPM indications of epilepsy, migraine, mood disorders, anxiety, chronic pain, obesity
    - No TPM within 120 days before or during pregnancy

Preliminary FORTRESS Results

- Oral clefts
  - **5 cases** in TPM monotherapy group
  - TPM monotherapy vs. Formerly Exposed cohort
    - **2.00 (95% CI, 0.71 - 5.68)**
  - TPM mono/polytherapy vs. Similar Medical Profile (SMP)
    - **2.7 (95% CI, 1.3 - 5.8)**
  - TPM monotherapy vs. SMP-No AED subgroup
    - **Not pre-specified**
    - **2.2 (95% CI, 0.9-5.4)**
- Major congenital malformations
  - Undergoing internal quality check

Study Limitations

- Live births only
  - No assessment for spontaneous/induced abortions or stillbirths
- Rare events of oral clefts
- Small sample size
  - Dose-response relationship could not be evaluated properly
  - Point estimates were unstable

Potential Sources of Bias and Impact

Direction of Bias	Study Limitations	S/C	Den	W-K	FOR
Underestimated Relative Risk	•Over-estimation of exposure		X	X	X
	•Composite OCs measure		X	X	X
	•Cases not validated		X	X	X
	•Misclassification of first trimester of pregnancy			X	X
Overestimated Relative Risk	•Possible recall bias	X			
Unknown Direction	•Residual confounding	X	X	X	X
	•TPM mono/poly therapy		X	X	
	•Reporting bias (covariates)	X			
	•Primary care setting was not included		X		

Summary Results for Oral Clefts

Slone/CDC	Denmark	Wolters Kluwer	FORTRESS	
No. of OC cases /No. of women exposed to TPM				
3,034 /**7**	**1** /108	**2** /870	**5** /1,740	
Estimated odds ratio/relative risk of OCs				
5.36 [a] (**1.49-20.07**)	5.45 (0.77-38.36)	1.47 [b] (0.36-6.06)	2.00 [c] (0.71-5.68)	**2.7** [d] (**1.3 - 5.8**)

a: Cleft lip with or without cleft palate

b: TPM vs. Migraine cohort

c: TPM monotherapy vs. FE cohort

d: TPM vs. SMP cohort

Summary Results for MCMs

Slone/CDC	Denmark	Wolters Kluwer	FORTRESS
No. of MCM cases/No. of women exposed to TPM			
33,605 /15	5 /108	37 /870	Pending
Estimated odds ratio/relative risk of MCMs			
1.01 (0.37-3.22)	1.44 (0.58-3.58)	1.12 [a] (0.81-1.55)	Pending

a: TPM vs. Migraine cohort

Conclusions

- No evidence for an increased risk of overall MCMs
- First-trimester TPM exposure is associated with an **increased risk of oral clefts**
- The estimated relative risks of OCs were **unstable**
  - Could range from 2 fold up to 5 fold based on currently available point estimates

Risk Management Options for Phentermine/Topiramate

Endocrinologic and Metabolic Drugs
Advisory Committee Meeting
February 22, 2012

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What is a REMS?

- Risk Evaluation and Mitigation Strategy (REMS)
  - A risk management plan that utilizes strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.
  - Designed to achieve specific goals to mitigate reported risks with a drug.
  - The Agency has authority to require a REMS in the pre-approval of a drug or post-approval.

What are the REMS Elements?

A REMS may include:

- Medication Guide - directed to patients
- Communication plan - directed to healthcare providers
- Elements to Assure Safe Use (ETASU)
  - A. Certification and training of prescribers
  - B. Certification of dispensers
  - C. Requirement that a drug be dispensed to patients only in certain health care settings
  - D. Documentation of safe use prior to dispensing a drug
  - E. Requirement for certain monitoring of a patient to receive a drug
  - F. Requirement that a patient enroll in a registry

A REMS for an NDA or BLA must include a timetable for submission of assessments of the REMS

ETASU Considerations

- A product can be approved only if an ETASU is put in place to mitigate the risk
- ETASU must be commensurate with specific serious risk(s) listed in the labeling
- ETASU cannot be unduly burdensome on patient access to drug, considering in particular, patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care
- To minimize the burden on the healthcare delivery system, ETASU must, to the extent practicable, conform with elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs

Using REMS to Mitigate Teratogenicity

- Goals of program
  - Prevent or minimize fetal exposures
  - Informing patients and healthcare providers of potential risks and requirements for safe use
- Risk Minimization Tools
  - Drug access linked to program requirements
  - Education-based program not linked to drug access

REMS for Teratogenicity

- REMS for PHEN/TPM under consideration to prevent or minimize teratogenic risk
- Six known or suspected human teratogens have approved REMS to address fetal exposure:
    - REMS with ETASU: ambrisentan, bosentan, isotretinoin, lenalidomide, thalidomide
    - REMS with a Medication Guide and communication plan: telavancin

Drugs with ETASU to Address Teratogenicity

- Ambrisentan and bosentan
  - Used for: pulmonary arterial hypertension
  - Teratogenicity: craniofacial, malformation of heart & great vessels, failure of formation of the thymus and thyroid
  - Data: Animal
  - ETASU: Certification of prescribers and dispensers, documentation of safe-use conditions; i.e., monthly pregnancy testing

Drugs with ETASU to Address Teratogenicity

- Lenalidomide and thalidomide
  - Used for: Multiple Myeloma, Myelodysplastic Syndromes, Erythema Nodosum Leprosum
  - Teratogenicity: Limb abnormalities
  - Data: lenalidomide-animal, thalidomide-human
  - ETASU: Certification of prescribers and dispensers, monthly pregnancy testing, patient registry

Drugs with ETASU to Address Teratogenicity

- Isotretinoin
  - Used for: Severe Recalcitrant Nodular Acne
  - Teratogenicity: Craniofacial, cleft palate, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit, cardiovascular, thymus gland, parathyroid hormone deficiency
  - Data: human
  - ETASU: Certification of prescribers and dispensers, monthly pregnancy testing, patient registry

Drugs with ETASU to Address Teratogenicity

- iPLEDGE program for isotretinoin studied in integrated health system
  - 2.67 pregnancies to females of childbearing potential (FCBP) per 1000 treatment courses

Shin J, Cheetham TC, et al. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system. J Am Acad Dermatol 2011.

PHEN/TPM Factors to Consider When Requiring a REMS

- Components, topiramate and phentermine available separately, including generics
- No REMS in place for components
- A very restrictive REMS for PHEN/TPM would likely increase use of separate components for weight loss

PHEN/TPM Factors to Consider When Requiring a REMS

- ETASU cannot be unduly burdensome on patient access to drug
- A restrictive REMS for Topamax/topiramate creates barriers for patients with other disorders

Risk Mitigation in the Clinical Trials

- Pregnancy prevention employed in clinical trials
- FCBP tested for pregnancy prior to beginning PHEN/TPM
- FCBP counseled about pregnancy prevention
- FCBP agreed to use double barrier or single barrier plus oral contraceptive pill (OCP), and were tested for pregnancy each month
- 34 pregnancies discovered at an average of 5.4 weeks gestation

REMS with Restrictive ETASU

- If a restrictive ETASU is required for PHEN/TPM
  - Topiramate, topiramate + phentermine could be used without the restrictions of the REMS
- If the same REMS is implemented for topiramate
  - patients with seizure disorders and migraine prophylaxis could be subjected to the same requirements

FDA Proposed REMS

- Medication Guide for patients
- Communication with all likely prescribers
  - Include patient counseling tools
- Prescriber training
  - Not linked to providers' ability to prescribe PHEN/TPM
- Distribution through certified pharmacies
- Periodic REMS assessments

FDA Proposed REMS

- Not disruptive to patients/prescribers using topiramate for other disorders
- Distribution allows for interaction with FCBP & collection of data regarding use
- Less likely to cause diversion of topiramate for weight loss

What is Not Included

- This REMS proposal does not include
  - Prescription contingent on mandatory monthly pregnancy testing for FCBP
  - Enrollment of prescribers
  - Enrollment of patients